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Attorney Docket No: 2094/1E286-US1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Jeffrey M. LINNEN and Kevin M. GORMAN

Serial No.: 09/493,353 Art Unit: 1655

Filed: January 28, 2000 Examiner: J. Goldberg

For: OLIGONUCLEOTIDE PRIMERS FOR EFFICIENT DETECTION OF HEPATITIS C VIRUS (HCV) AND METHODS OF USE THEREOF

RESPONSE TO OFFICE ACTION AND AMENDMENT UNDER 37 C.F.R. § 1.111

Hon. Commissioner of Patents and Trademarks
Washington, DC 20231

Sir:

In response to the Office Action mailed on October 12, 2000 in connection with the above-captioned patent application and in accordance with Rule 111 of the Rules of Practice, please enter the following amendments and consider the accompanying remarks.

The following amendments are made pursuant to the requirements of Rule 121 as revised in the new Rules of Practice. Accordingly, Applicants are

submitting herewith (1) a copy of the amended claims marked up, as required under 37 C.F.R. § 1.121(c)(ii), to show all changes relative to the previous version of each claim and attached hereto as Exhibit A. Applicants also submit herewith:

(2) Exhibit B: a copy of the reference "Enzymatic Amplification of DNA by PCR: Standard Procedures and Optimization" *Current Protocols in Molecular Biology* (Ausubel *et al.*, Eds.) Vol. 3, Chapter 15.1 (John Wiley & Sons, 1998) pages 15.1.1-15.1.15 ("Ausubel"), which is discussed in the below remarks;

(3) Exhibit C: a copy of the reference by Nolte *et al.*, "Preclinical Evaluation of AMPLICOR Hepatitis C Virus Test for Detection of Hepatitis C Virus RNA" *Journal of Clinical Microbiology* 1995, 33:1775-1778 ("Nolte"), which is discussed in the accompanying remarks;

(4) a Petition fo Extension of Time requesting an extension for a period of **two** months, from **January 12, 2001** up to and including **March 12, 2001**, accompanied by the appropriate fee; and

(3) an Amendment Fee Transmittal, accompanied by the appropriate fee.

It is believed that no additional fees are required for these submissions. However, should the U.S. Patent and Trademark Office determine that any additional fee is required or that any refund is due, the Commissioner is authorized to charge the required fee(s) and/or credit the refund(s) due to Deposit Account No. 04-0100.

Please amend the application as follows:

IN THE SPECIFICATION:

Enter the following paragraph immediately after the Title at line 1 on page 1 of the specification:

-- This application claims priority under 35 U.S.C. § 119(e) to U.S. Provisional Patent Application Serial No. 60/118,497 filed on February 3, 1999. --

IN THE CLAIMS:

Amend claims 1, 9-10, 22-23, 27, 35-36, 40-42 and 54 as indicated on the attached Exhibit A so that the claims are as follows:

1. (Amended) A method for detecting the presence of Hepatitis C Virus (HCV) RNA in a biological sample, said method comprising:

(A) performing a reverse transcription reaction using, as a template, RNA derived from said sample to produce HCV-specific reverse transcription products;

(B) amplifying said reverse-transcription products using one or more pairs of oligonucleotide primers specific for HCV to produce HCV-specific amplification products,

wherein said pairs are selected from the group consisting of:

(a) forward primer 5'-CAGAAAGCGTCTAGCCATGGCGTTAGTA-3' (C69F28) <SEQ ID NO. 1> and reverse primer 5'-CGGTTCCGCAGAGACCACTATGGCTCTC-3' (C133R26) <SEQ ID NO. 4>;

(b) forward primer 5'-GGGAGAGCCATAGTGGTCTGCGGAA-3' (C131F25) <SEQ ID NO. 2> and reverse primer 5'-CGGGGCACTCGCAAGCACCCTATCA-3' (C294R25) <SEQ ID NO. 7>; and

(c) forward primer 5'-GTGGTCTGCGGAACCGGTGAGTACAC-[3] 3' (C143F26) <SEQ ID NO. 3> and a reverse primer selected from the group consisting of

(i) 5'-GCAAGCACCCTATCAGGCAGTACCACA-3' (C282R27) <SEQ ID NO. 5>,

(ii) 5'-CACTCGCAAGCACCCTATCAGGCAGTA-3' (C287R27) <SEQ ID NO. 6>; and

(C) detecting said amplification products,

wherein detection of said amplification products indicates the presence of HCV RNA in said sample.

2. A method as defined in claim 1, wherein said reverse transcription reaction is performed using random oligonecleotide primers.

3. A method as defined in claim 1, wherein said reverse transcription reaction is performed using one or more oligonucleotide primers having sequences corresponding to sequences in HCV RNA.

4. A method as defined in claim 1, wherein said amplifying is performed by a method selected from the group consisting of polymerase chain reaction, ligase chain reaction, strand displacement amplification, nucleic acid single base substitution, and transcription mediated amplification.

5. A method as defined in claim 1, wherein said detecting comprises visualizing said amplification products by gel electrophoresis.

6. A method as defined in claim 1, wherein said detecting comprises capturing said amplification products on a solid support containing one or more HCV-specific oligonucleotide probes and quantifying said captured products using a colorimetric assay.

7. A method as defined in claim 6, wherein said probes comprise a member selected from the group consisting of:

(a) 5'-TTTCGCGACCCAACACTACTCGGCT-3' (C252-25-PRB) <SEQ ID NO. 13> and

(b) 5'-CCTTTCGCGACCCAACACTACTCGGCT-3' (C252-27-PRB) <SEQ ID NO. 12> when said forward primer is (C131F25) or (C143F26); and

wherein said probes comprise

(c) 5'-GGGTCCTGGAGGCTGCACGACACTCAT-3' (C96-22-PRB) <SEQ ID NO. 11> when said forward primer is (C69F28).

8. A method as defined in claim 1, wherein said sample is selected from the group consisting of blood, serum, plasma, urine, saliva, and cerebrospinal fluid.

Sub D2

9. (Amended) A method for amplifying Hepatitis C Virus (HCV) DNA, which method comprises performing a polymerase chain reaction on a DNA sample containing HCV DNA using one or more pairs of oligonucleotide primers specific for HCV to produce HCV-specific amplification products, wherein said pairs are selected from the group consisting of:

(a) forward primer 5'-CAGAAAGCGTCTAGCCATGGCGTTAGTA-3' (C69F28) <SEQ ID NO. 1> and reverse primer 5'-CGGTTCCGCAGACCACTATGGCTCTC-3' (C133R26) <SEQ ID NO. 4>;

(b) forward primer 5'-GGGAGAGCCATAGTGGTCTGCGGAA-3' (C131F25) <SEQ ID NO. 2> and reverse primer 5'-CGGGGCACTCGCAAGCACCCTATCA-3' (C294R25) <SEQ ID NO. 7>; and

(c) forward primer 5'-GTGGTCTGCGGAACCGGTGAGTACAC-3 (C143F26) <SEQ ID NO. 3> and a reverse primer selected from the group consisting of

(i) 5'-GCAAGCACCCTATCAGGCAGTACCACA-3' (C282R27) <SEQ ID NO. 5>,

(ii) 5'-CACTCGCAAGCACCCTATCAGGCAGTA-3' (C287R27) <SEQ ID NO. 6>.

10. (Amended) A method as defined in claim 9, which method further comprises detecting said amplification products, wherein detection of said amplification products indicates the presence of HCV DNA in said sample.

11. A method as defined in claim 10, wherein said detecting comprises visualizing said amplification products by gel electrophoresis.

12. A method as defined in claim 10, wherein said detecting comprises capturing said amplification products on a solid support containing one or more HCV-

specific oligonucleotide probes and quantifying said captured products using a colorimetric assay.

13. A method as defined in claim 10, wherein said probes comprise a member selected from the group consisting of:

(a) 5'-TTTCGCGACCCAACACTACTCGGCT-3' (C252-25-PRB) <SEQ ID NO. 13> and

(b) 5'-CCTTTCGCGACCCAACACTACTCGGCT-3' (C252-27-PRB) <SEQ ID NO. 12> when said forward primer is (C131F25) or (C143F26); and

wherein said probes comprise

(c) 5'-GGGTCCTGGAGGCTGCACGACACTCAT-3' (C96-22-PRB) <SEQ ID NO. 11> when said forward primer is (C69F28).

14. A method for detecting the presence of Hepatitis C Virus (HCV) RNA in a biological sample, said method comprising:

(A) performing a reverse transcription reaction using as a template RNA derived from said sample to produce HCV-specific reverse transcription products;

(B) amplifying said reverse-transcription products using a forward primer and a reverse primer to produce HCV-specific amplification

products, wherein said forward primer consists of the oligonucleotide 5'-GGTGGCTCCATCTTAGCCCTAGTCACG-3' (1F27) <SEQ ID NO. 8> and said reverse primer consists of the oligonucleotide 5'-AGGCCAGTATCAGCACTCTCTGCAGTC-3' (57R27) <SEQ ID NO. 9>; and

(C) detecting said amplification products,

wherein detection of said amplification products indicates the presence of HCV RNA in said sample.

15. A method as defined in claim 14, wherein said reverse transcription reaction is performed using random oligonucleotide primers.

16. A method as defined in claim 14, wherein said reverse transcription reaction is performed using one or more oligonucleotide primers having sequences corresponding to sequences in HCV RNA.

17. A method as defined in claim 14, wherein said amplifying is performed by a method selected from the group consisting of polymerase chain reaction, ligase chain reaction, strand displacement amplification, nucleic acid single base substitution, and transcription mediated amplification.

18. A method as defined in claim 14, wherein said detecting comprises visualizing said amplification products by gel electrophoresis.

19. A method as defined in claim 14, wherein said detecting comprises capturing said amplification products on a solid support containing one or more HCV-specific oligonucleotide probes and quantifying said captured products using a colorimetric assay.

20. A method as defined in claim 19, wherein said probes are selected from the group consisting of 5'-GCGGCTCACGGACCTTTCACAGCTA-3' (30PRB25) <SEQ ID NO. 14> and 5'-ATGCGGCTCACGGACCTTTCACAGC-3' (32PRB25) <SEQ ID NO. 15>.

21. A method as defined in claim 14, wherein said sample is selected from the group consisting of blood, serum, plasma, urine, saliva, and cerebrospinal fluid.

22. (Amended) A method for amplifying Hepatitis C Virus (HCV) DNA, which method comprises performing a polymerase chain reaction on a DNA sample containing HCV DNA using a forward primer and a reverse primer to produce HCV-specific amplification products, wherein said forward primer consists of the oligonucleotide 5'-GGTGGCTCCATCTTAGCCCTAGTCACG- 3' (1F27) <SEQ ID NO.

8> and said reverse primer consists of the oligonucleotide 5'-AGGCCAGTATCAGCACTCTCTGCAGTC-3' (57R27) <SEQ ID NO. 9>.

23. (Amended) A method as defined in claim 22, which method further comprises detecting said amplification products, wherein detection of said amplification products indicates the presence of HCV DNA in said sample.

24. A method as defined in claim 23, wherein said detecting comprises visualizing said amplification products by get electrophoresis.

25. A method as defined in claim 23, wherein said detecting comprises capturing said amplification products on a solid support containing one or more HCV-specific oligonucleotide probes and quantifying said captured products using a colorimetric assay.

26. A method as defined in claim 25, wherein said probes are selected from the group consisting of 5'-GCGGCTCACGGACCTTTCACAGCTA-3' (30PRB25) <SEQ ID NO. 14> and 5'-ATGCGGCTCACGGACCTTTCACAGC-3' 32PRB25) <SEQ ID NO. 15>.

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27. (Amended) A method for detecting the presence of Hepatitis C Virus (HCV) RNA in a biological sample, said method comprising:

(A) performing a reverse transcription reaction using as a template RNA derived from said sample to produce HCV-specific reverse transcription products;

(B) amplifying said reverse-transcription products using one or more pairs of 5' NCR oligonucleotide primers specific for HCV and one or more pairs of 3' NCR oligonucleotide primers to produce HCV-specific amplification products,

wherein said 5' NCR primer pairs are selected from the group consisting of:

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(a) forward primer 5'-CAGAAAGCGTCTAGCCATGGCGTTAGTA-3' (C69F28) <SEQ ID NO. 1> and reverse primer 5'-CGGTTCCGCAGACCACTATGGCTCTC-3' (C133R26) <SEQ ID NO. 4>;

(b) forward primer 5'-GGGAGAGCCATAGTGGTCTGCGGAA-3' (C131F25) <SEQ ID NO. 2> and reverse primer 5'-CGGGGCACTCGCAAGCACCCTATCA-3' (C294R25) <SEQ ID NO. 7>; and

(c) forward primer 5'-GTGGTCTGCGGAACCGGTGAGTACAC-3' (C143F26) <SEQ ID NO.3> and a reverse primer selected from the group consisting of

(i) 5'-GCAAGCACCCTATCAGGCAGTACCACA-3' (C282R27) <SEQ ID NO. 5>,

(ii) 5'-CACTGGCAAGCACCCTATCAGGCAGTA-3' (C287R27) <SEQ ID NO. 6>; and

wherein each of said pairs of 3' NCR oligonucleotide primers comprises a forward primer consisting of the oligonucleotide 5'-GGTGGCTCCATCTTAGCCCTAGTCACG-3' (1F27) <SEQ ID NO. 8> and a reverse primer consisting of the oligonucleotide 5'-AGGCCAGTATCAGCACTCTCTGCAGTC-[3] 3' (57R27) <SEQ ID NO. 9>; and

(C) detecting said amplification products,

wherein detection of said amplification products indicates the presence of HCV RNA in said sample.

28. A method as defined in claim 27, wherein said reverse transcription reaction is performed using random oligonucleotide primers.

29. A method as defined in claim 27, wherein said reverse transcription reaction is performed using one or more oligonucleotide primers having sequences corresponding to sequences in HCV RNA.

30. A method as defined in claim 27, wherein said amplifying is performed by a method selected from the group consisting of polymerase chain reaction, ligase chain reaction, strand displacement amplification, nucleic acid single base substitution, and transcription mediated amplification.

31. A method as defined in claim 27, wherein said detecting comprises visualizing said amplification products by gel electrophoresis.

32. A method as defined in claim 27, wherein said detecting comprises capturing said amplification products on a solid support containing one or more HCV-specific oligonucleotide probes and quantifying said captured products using a colorimetric assay.

33. A method as defined in claim 32, wherein said probes comprise a member selected from the group consisting of:

(a) 5'-TTTCGCGACCCAACACTACTCGGCT-3' (C252-25-PRB) <SEQ ID NO. 13> and

(b) 5'-CCTTTCGCGACCCAACACTACTCGGCT-3' (C252-27-PRB) <SEQ ID NO. 12> when said 5' NCR forward primer is (C131F25) or (C143F26);

wherein said probes comprise

(c) 5'-GGGTCCTGGAGGCTGCACGACACTCAT-3' (C96-22-PRB) <SEQ ID NO. 11> when said 5' NCR forward primer is (C69F28); and

wherein said probes comprise a member selected from the group consisting of

(d) 5'-GCGGCTCACGGACCTTTCACAGCTA-3' (30PRB25) <SEQ ID NO. 14>; and

(e) 5'-ATGCGGCTCACGGACCTTTCACAGC-3' (32PRB25) <SEQ ID NO. 15>.

34. A method as defined in claim 27, wherein said sample is selected from the group consisting of blood, serum, plasma, urine, saliva, and cerebrospinal fluid.

Sub D4

35. (Amended) A method for amplifying Hepatitis C Virus (HCV) DNA, which method comprises performing a polymerase chain reaction on a DNA sample containing HCV DNA using one or more pairs of 5' NCR oligonucleotide primers specific for HCV and one or more pairs of 3' NCR oligonucleotide primers to produce HCV-specific amplification products,

wherein said 5' NCR primer pairs are selected from the group consisting of:

(a) forward primer 5'-CAGAAAGCGTCTAGCCATGGCGTTAGTA-3' (C69F28) <SEQ ID NO. 1> and reverse primer 5'-CGGTTCCGCAGACCACTATGGCTCTC-3' (C133R26) <SEQ ID NO. 4>;

(b) forward primer 5'-GGGAGAGCCATAGTGGTCTGCGGAA-3' (C131F25) <SEQ ID NO. 2> and reverse primer 5'-CGGGGCACTCGCAAGCACCCTATCA-3' (C294R25) <SEQ ID NO. 7>; and

(c) forward primer 5'-GTGGTCTGCGGAACCGGTGAGTACAC-3' (C143F26) <SEQ ID NO. 3> and a reverse primer selected from the group consisting of

(i) 5'-GCAAGCACCCTATCAGGCAGTACCACA-3' (C282R27) <SEQ ID NO. 5>,

(ii) 5'-CACTCGCAAGCACCCTATCAGGCAGTA-3' (C287R27) <SEQ ID NO. 6>; and

wherein each of said pairs of 3' NCR oligonucleotide primers comprises a forward primer consisting of the oligonucleotide 5'-GGTGGCTCCATCTTAGCCCTAGTCACG-3' (1F27) <SEQ ID NO. 8> and a reverse primer consisting of the oligonucleotide 5'-AGGCCAGTATCAGCACTCTCTGCAGTC-3' (57R27) <SEQ ID NO. 9>.

36. (Amended) A method as defined in claim 35, which method further comprises detecting said amplification products, wherein detection of said amplification products indicates the presence of HCV DNA in said sample.

37. A method as defined in claim 36, wherein said detecting comprises visualizing said amplification products by gel electrophoresis.

38. A method as defined in claim 36, wherein said detecting comprises capturing said amplification products on a solid support containing one or more HCV-specific oligonucleotide probes and quantifying said captured products using a colorimetric assay.

39. A method as defined in claim 38, wherein said probes comprise a member selected from the group consisting of:

(a) 5'-TTTCGCGACCCAACACTACTCGGCT-3' (C252-25-PRB) <SEQ ID NO. 13> and

(b) 5'-CCTTTCGCGACCCAACACTACTCGGCT-3' (C252-27PRB) <SEQ ID NO. 12> when said 5' NCR forward primer is (C131F25) or (C143F26);

wherein said probes comprise

(c) 5'-GGGTCCTGGAGGCTGCACGACACTCAT-3' (C96-22-PRB) <SEQ ID NO. 11> when said 5' NCR forward primer is (C69F28); and

wherein said probes comprise a member selected from the group consisting of

(d) 5'-GCGGCTCACGGACCTTTCACAGCTA-3' (30PRB25) <SEQ ID NO. 14>; and

(e) 5'-ATGCGGCTCACGGACCTTTCACAGC-3' (32PRB25) <SEQ ID NO. 15>.

Sub D5

40. (Amended) An oligonucleotide selected from the group consisting of:

5'-CAGAAAGCGTCTAGCCATGGCGTTAGTA-3' (C69f28) <SEQ ID NO. 1>;

5'-GGGAGAGCCATAGTGGTCTGCGGAA-3' (C131F25) <SEQ ID NO. 2>;

5'-GTGGTCTGCGGAACCGGTGAGTACAC-3 (C143F26) <SEQ ID NO. 3>;

5'-CGGTTCCGCAGACCACTATGGCTCTC-3 (C133R26) <SEQ ID NO. 4>;

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5'-CACTCGCAAGCACCCTATCAGGCAGTA-3' (C287R27) <SEQ ID NO. 6>;

5'-CGGGGCACTCGCAAGCACCCTATCA-3' (C294R25) <SEQ ID NO. 7>;

5'-GGTGGCTCCATCTTAGCCCTAGTCACG-3' (1F27) <SEQ ID NO. 8>;

5'-AGGCCAGTATCAGCACTCTCTGCAGTC-3 (57R27) <SEQ ID NO. 9>;

5'-GGGTCCTGGAGGCTGCACGACACTCAT-3' (C96-22-PRB) <SEQ ID NO. 11>;

5'-CCTTTCGCGACCCAACACTACTCGGCT-3' (C252-27-PRB) <SEQ ID NO. 12>;

5'-TTTCGCGACCCAACACTACTCGGCT-3' (C252-25-PRB) <SEQ ID NO. 13>;

5'-GCGGCTCACGGACCTTTCACAGCTA-3' (30PRB25) <SEQ ID NO. 14>; and

5'-ATGCGGCTCACGGACCTTTCACAGC-3' (32PRB25) <SEQ ID NO. 15>.

41. (Amended) An HCV-specific amplification primer oligonucleotide selected from the group consisting of:

5'-CAGAAAGCGTCTAGCCATGGCGTTAGTA-3' (C69F28) <SEQ ID NO. 1>;

5'-GGGAGAGCCATAGTGGTCTGCGGAA-3' (C131F25) <SEQ ID NO. 2>;

5'-GTGGTCTGCGGAACCGGTGAGTACAC-3' (C143F26) <SEQ ID NO. 3>;

5'-CGGTTCCGCAGACCACTATGGCTCTC-3' (C133R26) <SEQ ID NO. 4>;

5'-CACTCGCAAGCACCCTATCAGGCAGTA-3' (C287R27) <SEQ ID NO. 6>;

5'-CGGGGCACTCGCAAGCACCCTATCA-3' (C294R25) <SEQ ID NO. 7>;

5'-GGTGGCTCCATCTTAGCCCTAGTCACG-3' (1F27) <SEQ ID NO. 8>; and

5'-AGGCCAGTATCAGCACTCTCTGCAGTC-3' (57R27) <SEQ ID NO. 9>.

42. (Amended) An oligonucleotide probe comprising a sequence selected from the group consisting of:

5'-GGGTCCTGGAGGCTGCACGACACTCAT-3' (C96-22-PRB) <SEQ ID NO. 11>;

5'-CCTTTCGCGACCCAACACTACTCGGCT-3' (C252-27-PRB) <SEQ ID NO. 12>;

5'-TTTCGCGACCCAACACTACTCGGCT-3' (C252-25-PRB) <SEQ ID NO. 13>;

5'-GCGGCTCACGGACCTTTCACAGCTA-3' (30PRB25) <SEQ ID NO. 14>; and

5'-ATGCGGCTCACGGACCTTTCACAGC-3' (32PRB25) <SEQ ID NO. 15>.

43. A kit for amplying HCV DNA derived from HCV RNA, said kit comprising one or more pairs of 5' NCR oligonucleotide primers, wherein said 5' NCR primer pairs are selected from the group consisting of:

(a) forward primer 5'-CAGAAAGCGTCTAGCCATGGCGTTAGTA-3' (C69F28) <SEQ ID NO. 1> and reverse primer 5'-CGGTTCCGCAGACCACTATGGCTCTC-3' (C133R26) <SEQ ID NO. 4>;

(b) forward primer 5'-GGGAGAGCCATAGTGGTCTGCGGAA-3' (C131F25) <SEQ ID NO. 2> and reverse primer 5'-CGGGGCACTCGCAAGCACCCTATCA-3' (C294R25) <SEQ ID NO. 7>; and

(c) forward primer 5'-GTGGTCTGCGGAACCGGTGAGTACAC-3 (C143F26) <SEQ ID NO. 3> and a reverse primer selected from the group consisting of

(i) 5'-GCAAGCACCCTATCAGGCAGTACCACA-3' (C282R27) <SEQ ID NO. 5>,

(ii) 5'-CACTCGAAGCACCCTATCAGGCAGTA-3' (C287R27) <SEQ ID NO. 6>.

44. A kit as defined in claim 43, further comprising one or more pairs of 3' NCR oligonucleotide primers, wherein each of said pairs of 3' NCR oligonucleotide primers comprises a forward primer consisting of the oligonucleotide 5'-GGTGGCTCCATCTTAGCCCTAGTCACG-3' (1F27) <SEQ ID NO. 8> and a reverse primer consisting of the oligonucleotide 5'-AGGCCAGTATCAGCACTCTCTGCAGTC-3 (57R27) <SEQ ID NO. 9>.

45. A kit as defined in claim 43, further comprising one or more probes.

46. A kit as defined in claim 44, further comprising one or more probes.

47. A kit as defined in claim 45, wherein said probes comprise a member selected from the group consisting of:

(a) 5'-TTTCGCGACCCAACACTACTCGGCT-3' (C252-25-PRB) <SEQ ID NO. 13> and

(b) 5'-CCTTTCGCGACCCAACACTACTCGGCT-3' (C252-27-PRB) <SEQ ID NO. 12> when said 5' NCR forward primer is (C131F25) or (C143F26); and

wherein said probes comprise

(c) 5'-GGGTCCTGGAGGCTGCACGACACTCAT-3' (C96-22-PRB) <SEQ ID NO. 11> when said 5' NCR forward primer is (C69F28).

48. A kit as defined in claim 46, wherein said probes comprise a member selected from the group consisting of:

(a) 5' -TTTCGCGACCCAACACTACTCGGCT-3' (C252-25-PRB) <SEQ ID NO. 13> and

(b) 5'-CCTTCGCGACCCAACACTACTCGGCT-3' (C252-27-PRB) <SEQ ID NO. 12> when said 5' NCR forward primer is (C131F25) or (C143F26);

wherein said probes comprise

(c) 5'-GGGTCCTGGAGGCTGCACGACACTCAT-3' (C96-22-PRB) <SEQ ID NO. 11> when said 5' NCR forward primer is (C69F28); and

wherein said probes comprise a member selected from the group consisting of

(d) 5'-GCGGCTCACGGACCTTTCACAGCTA-3' (30PRB25) <SEQ ID NO. 14>; and

(e) 5'-ATGCGGCTCACGGACCTTTCACAGC-3' (32PRB25) <SEQ ID NO. 15>.

49. A kit as defined in claim 43, wherein said pair of 5' NCR primers consists of 5'-CAGAAAGCGTCTAGCCATGGCGTTAGTA-3' (C69F28) <SEQ ID NO. 1> and 5'-CGGTTCCGCAGACCACTATGGCTCTC-3' (C133R26) <SEQ ID NO. 4>.

50. A kit as defined in claim 43, wherein said pair of 5' NCR primers consists of 5'-GGGAGAGCCATAGTGGTCTGCGGAA-3' (C131F25) <SEQ ID NO. 2> and 5'-CGGGGCACTCGCAAGCACCCTATCA-3' (C294R25) <SEQ ID NO. 7>.

51. A kit for amplifying HCV cDNA derived from HCV RNA, said kit comprising one or more pairs of 3' NCR oligonucleotide primers, wherein each of said pairs of 3' NCR oligonucleotide primers comprises a forward primer consisting of the oligonucleotide 5'-GGTGGCTCCATCTTAGCCCTAGTCACG-3' (1F27) <SEQ ID NO. 8> and a reverse primer consisting of the oligonucleotide 5'-AGGCCAGTATCAGCACTCTCTGCAGTC-[3] 3' (57R27) <SEQ ID NO. 9>.

52. A kit as defined in claim 51, further comprising one or more probes.

53. A kit as defined in claim 52, wherein said probes are selected from the group consisting of:

(a) 5'-GCGGCTCACGGACCTTTCACAGCTA-3' (30PRB25) <SEQ ID NO. 14>; and

(b) 5'-ATGCGGCTCACGGACCTTTCACAGC-3' (32PRB25) <SEQ ID NO. 15>.

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54. (Amended) A kit for detecting the presence of HCV DNA, said kit comprising one or more pairs of 5' NCR oligonucleotide primers, wherein said 5' NCR primer pairs are selected from the group consisting of:

(a) forward primer 5'-CAGAAAGCGTCTAGCCATGGCGTTAGTA-3' (C69F28) <SEQ ID NO. 1> and reverse primer 5'-CGGTTCCGCAGACCACTATGGCTCTC-3' (C133R26) <SEQ ID NO. 4>;

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(b) forward primer 5'-GGGAGAGCCATAGTGGTCTGCGGAA-3' (C131F25) <SEQ ID NO. 2> and reverse primer 5'-CGGGGCACTCGCAAGCACCCTATCA-3' (C294R25) <SEQ ID NO. 7>; and

(c) forward primer 5'-GTGGTCTGCGGAACCGGTGAGTACAC-[3] 3' (C143F26) <SEQ ID NO. 3> and a reverse primer selected from the group consisting of

(i) 5'-GCAAGCACCCTATCAGGCAGTACCACA-3' (C282R27) <SEQ ID NO. 5>,

(ii) 5'-CACTCGCAAGCACCCTATCAGGCAGTA-3' (C287R27) <SEQ ID NO. 6>.

55. A kit as defined in claim 54, further comprising one or more pairs of 3' NCR oligonucleotide primers, wherein each of said pairs of 3' NCR oligonucleotide primers comprises a forward primer consisting of the oligonucleotide 5'-GGTGGCTCCATCTTAGCCCTAGTCACG-3' (1F27) <SEQ ID NO. 8> and a reverse primer consisting of the oligonucleotide 5'-AGGCCAGTATCAGCACTCTCTGCAGTC-3 (57R27) <SEQ ID NO. 9>.

56. A kit as defined in claim 54, further comprising one or more probes.

57. A kit as defined in claim 55, further comprising one or more probes.

58. A kit as defined in claim 56, wherein said probes comprise a member selected from the group consisting of:

(a) 5'-TTTCGCGACCCAACACTACTACTCGGCT- 3' (C252-25-PRB) <SEQ ID NO. 13> and

(b) 5'-CCTTTCGCGACCCAACACTACTCGGCT- 3' (C252-27-PRB) <SEQ ID NO. 12> when said 5' NCR forward primer is (C131F25) or (C143F26);

wherein said probes comprise

(c) 5' -GGGTCCTGGAGGCTGCACGACACTCAT-3' (C96-22-PRB) <SEQ ID NO. 11> when said 5' NCR forward primer is (C69F28).

59. A kit as defined in claim 57, wherein said probes comprise a member selected from the group consisting of:

(a) 5'-TTTCGCGACCCAACACTACTCGGCT-3' (C252-25-PRB) <SEQ ID NO. 13> and

(b) 5'-CCTTTCGCGACCCAACACTACTCGGCT-3' (C252-27-PRB) <SEQ ID NO. 12> when said 5' NCR forward primer is (C131F25) or (C143F26);

wherein said probes comprise

(c) 5'-GGGTCCTGGAGGCTGCACGACACTCAT-3' (C96-22-PRB) <SEQ ID NO. 11> when said 5' NCR forward primer is (C69F28); and

wherein said probes comprise a member selected from the group consisting of

(d) 5'-GCGGCTCACGGACCTTTCACAGCTA-3' (30PRB25) <SEQ ID NO. 14>; and

(e) 5'-ATGCGGCTCACGGACCTTTCACAGC-3' (32PRB25) <SEQ ID NO. 15>.

60. A kit as defined in claim 54, wherein said pair of 5' NCR primers consists of 5'-CAGAAAGCGTCTAGCCATGGCGTTAGTA-3' (C69F28) <SEQ ID NO. 1> and 5'-CGGTTCCGCAGACCACTATGGCTCTC-3' (C133R26) <SEQ ID NO. 4>.

61. A kit as defined in claim 54, wherein said pair of 5' NCR primers consists of 5'-GGGAGAGCCATAGTGGTCTGCGGAA- 3' (C131F25) <SEQ ID NO. 2> and 5'-CGGGGCACTCGCAAGCACCCTATCA- 3' (C294R25) <SEQ ID NO. 7>.

62. A kit for detecting the presence of HCV RNA, said kit comprising one or more pairs of 3' NCR oligonucleotide primers, wherein each of said pairs of 3' NCR oligonucleotide primers comprises a forward primer consisting of the oligonucleotide 5'-GGTGGCTCCATCTTAGCCCTAGTCACG-3' (1F27) <SEQ ID NO. 8> and a reverse primer consisting of the oligonucleotide 5'-AGGCCAGTATCAGCACTCTCTGCAGTC-3 (57R27) <SEQ ID NO. 9>.

63. A kit as defined in claim 62, further comprising one or more probes.

64. A kit as defined in claim 63, wherein said probes are selected from the group consisting of 5'-GCGGCTCACGGACCTTTCACAGCTA-3' (30PRB25) <SEQ ID NO. 14> and 5'-ATGCGGCTCACGGACCTTTCACAGC-3' (32PRB25) <SEQ ID NO. 15>.

REMARKS

Claims 1-64 are pending in this application. Claims 1, 9-10, 22-23, 27, 35-36, 40-42 and 54 have been amended without prejudice. Specifically, claims 1, 9-10, 22-23, 27, 35-36 and 54 have been amended merely to clarify the language of those claims and/or to correct improper Markush claim language discovered by Applicants upon review of the pending claims. Claim 42 has also been amended to clarify the language of the claim and to more particularly point out the claimed subject matter of Applicants' invention. In particular, the preamble of claim 42 has been amended to specifically recite an *oligonucleotide* probe. Finally, claims 40-41 have been amended to remove the recitation of nucleic acid SEQ ID NO:5 recited in those claims. This amendment is made without admission or prejudice, and Applicants reserve the right to pursue claims reciting SEQ ID NO:5 in both the instant and in other (*e.g.*, related) patent applications.

Finally, the specification has also been amended to include a specific reference to the provisional patent application (*i.e.*, Serial No. 60/118,497) to which priority is claimed as required under 37 C.F.R. § 1.78.

The above amendments have been made pursuant to the requirements of Rule 121 of the Rules of Practice. Specifically, the pending claims are written above in clean form and in accordance with 37 C.F.R. § 1.121(c)(1)(i) and § 1.121(c)(3). Pursuant to the requirements of 37 C.F.R.§ 1.121(c)(1)(ii), another version of the amended claims is attached hereto as Exhibit A. This other version has been marked up to show all changes made in this amendment relative to the previous version of each claim. As explained above, the amendments do not constitute new matter. Entry and consideration of the amendments is therefore respectfully requested.

THE REJECTIONS UNDER 35 U.S.C. § 102 SHOULD BE WITHDRAWN

Claims 1-2, 4-6, 9-12, 43, 45, 54 and 56 have been rejected under 35 U.S.C. § 102(e) as anticipated by U.S. Patent No. 5,846,704 issued December 8, 1998 to Maertens *et al.* ("Maertens"). In addition, claims 40-41 have been rejected under 35 U.S.C. § 102(e) as anticipated by U.S. Patent No. 5,837,422 issued November 17, 1998 to Tsang ("Tsang"), and claim 42 has been rejected under 35 U.S.C. § 102(b)[1] as anticipated by both Han *et al.*, "Characterization of the Terminal Regions of Hepatitis C Viral RNA: Identification of Conserved Sequences in the 5' Untranslated Region and Poly(A) Tails at the 3' End", *Proc. Natl. Acad. Sci. U.S.A.* 1991, 88:1711-1715 ("Han")

[1] The Office Action actually indicates that claim 42 is rejected under 35 U.S.C. § 102(e) as anticipated by Han and Kolykhalov. However, 35 U.S.C. § 102(e) is actually for anticipation rejections where "the invention was described in a *patent*". 35 U.S.C. § 102(e) (emphasis added). Applicants therefore assume that the Examiner intends 35 U.S.C. § 102(b) when rejecting claim 42 as anticipated by the non-patent publications of Han and Kolykhalov.

and Kolykhalov *et al.*, "Identification of a Highly Conserved Sequence Element at the 3' Terminus of Hepatitis C Virus Genome RNA", *J. of Virology* 1996, 70(6):3363-3371 ("Kolykhalov"). Each of these rejections is discussed in turn below.

Anticipation requires that each and every element of the rejected claim(s) be disclosed in a single prior art reference. See, M.P.E.P. § 2131. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Every element of the claimed invention must be literally present, arranged as in the claim. *Perkin Elmer Corp.* 732 F.2d 888, 894, 221 USPQ 669, 673.

In the present instance, the relevant inquiry is whether a single reference discloses: (i) oligonucleotides (including oligonucleotide primers and probes) having the particular nucleotide sequences recited in the pending claims of this application; (ii) methods using these particular oligonucleotides to detect and amplify HCV; and (iii) kits that contain these particular oligonucleotide probes and primers. As explained in detail below, none of the references cited by the Examiner discloses any of these elements. Accordingly, the rejections under 35 U.S.C. § 102 should be withdrawn.

A. *The Maertens patent does not anticipate the present invention:*

Claims 1-2, 4-6, 9-12, 43, 45, 54 and 56 have been rejected under 35 U.S.C. § 102(e) as anticipated by U.S. Patent No. 5,846,704 issued December 8, 1998

to Maertens *et al.* ("Maertens"). In particular, the Office Action indicates that Maertens teaches certain nucleic acid primers (denoted in Maertens by SEQ ID NOS:3 and 4) that overlap primers of the present invention (specifically, the primers denoted in this application by SEQ ID NOS:3, 5 and 6) by at least 15 contiguous nucleotides. The Office Action also notes that Maertens includes a claim (claim 11) reciting a method for genotyping HCV in a biological sample. In particular, the method recited in claim 11 of Maertens uses "inner primers" that hybridize to the particular primers denoted by SEQ ID NOS:3 and 4 in Maertens. Contrary to what is stated in the Office Action, however, Maertens does not teach the limitations of the presently claimed invention. In particular, Maertens does not teach <u>any</u> of the particular oligonucleotide sequences recited in the pending claims, let alone particular probes or primers having any of those specific sequences.

The Office Action appears to suggest that Maertens anticipates claims of this application because specific oligonucleotide primers recited in those claims might be used in a method recited in claim 11 of Maertens. Thus, the claims are apparently rejected because the Examiner considers claim 11 of Maertens broad enough to encompass specific primers of this invention and not because Maertens actually discloses those particular primers. This analysis, however, is not the correct standard for anticipation. "The scope of a patent's claims determines what infringes a patent; it is by no means a measure of what it discloses." *In re Benno* 788 F.2d 1340, 1346, 226 USPQ 638, 686 (Fed. Cir. 1985). "A patent discloses only that which it describes,

whether specifically or in general terms, so as to convey intelligence to one capable of undertsanding." *Ibid.* See, also, *Corning Glass Works v. Sumitomo Electric U.S.A.*, 868 F.2d 1251, 1262, 9 USPQ2d 1962, 1970 (Fed. Cir. 1989).

As explained above, Maertens does not disclose any oligonucleotide having a specific nucleic acid sequence recited in the pending claims of this application. At best Maertens only describes some primers that partially overlap the oligonucleotide sequence of this invention. Nevertheless, the sequences taught by Maertens are distinct from, and therefore cannot anticipate, the particular sequences of this invention.

B. *The pending claims are not anticipated by the Tsang patent:*

Claims 40-41 have been rejected under 35 U.S.C. § 102(e) as anticipated by U.S. Patent No. 5,837,422 issued November 17, 1998 to Tsang ("Tsang"). The Office Action indicates, specifically, that this patent discloses an oligonucleotide sequence (GCAAGCACCCTATCAGGCAGTACCACA; SEQ ID NO:3 in Tsang) that is 100% identical to the sequence provided in SEQ ID NO:5 of this application. Applicants note, however, that claims 40-41 have been amended *supra* and do not recite an oligonucleotide having the sequence set forth in SEQ ID NO:5 of this application. As such, the rejection of these claims under 35 U.S.C. § 102(e) has been obviated and should be withdrawn.

C. *The references of Han and Kolykhalov do not anticipate the pending claims:*

Claim 42 has been rejected under 35 U.S.C. § 102(b) as being anticipated by the reference Han *et al.*, "Characterization of the Terminal Regions of Hepatitis C Viral RNA: Identification of Conserved Sequences in the 5' Untranslated Region and Poly(A) Tails at the 3' End" *Proc. Natl. Acad. Sci. U.S.A.* 1991, 88:1711-1715 ("Han"). Claim 42 has also been rejected under 35 U.S.C. § 102(b) as anticipated by the reference Kolykhalov *et al.*, "Identification of a Highly Conserved Sequence Element at the 3' Terminus of Hepatitis C Virus Genome RNA" *J. of Virology* 1996, 70(6):3363-3371 ("Kolykhalov"). These references allegedly teach large regions of the HCV genomic sequence that have certain oligonucleotide sequences of this invention embedded therein.

In response, Applicants note that claim 42 has been amended *supra* to more particularly recite an *oligonucleotide* probe. Han and Kolykhalov, however, merely describe large genomic sequences of the Hepatitis C virus and do not describe any oligonculeotide probes, let alone any of the specific oligonucleotide probes of this invention. Accordingly, the rejections of claim 42 under 35 U.S.C. § 102(b) have been obviated and should be withdrawn.

THE REJECTIONS UNDER 35 U.S.C. § 103(a) SHOULD BE WITHDRAWN

The pending claims of this application have also been rejected under 35 U.S.C. § 103(a) as obvious over various references cited in the Office Action. In particular, the claims have been rejected as follows:

(1) Claims 1, 3-13 and 40-42 have been rejected as obvious over Han *et al.*, "Characterization of the Terminal Regions of Hepatitis C Viral RNA: Identification of Conserved Sequences in the 5' Untranslated Region and Poly(A) Tails at the 3' End", *Proc. Natl. Acad. Sci. U.S.A.* 1991, 88:1711-1715 ("Han");

(2) Claims 43, 45, 47, 49-50, 54, 56, 58 and 60-61 have been rejected as obvious of Han in further view of Ahern, "Biochemical Reagent Kits Offer Scientists Good Return on Investment", *The Scientist* 1995, 9(15):20 ("Ahern")[2];

(3) Claims 14, 16-26 and 40-42 have been rejected as obvious over Kolykhalov *et al.*, "Identification of a Highly Conserved Sequence Element at the 3' Terminus of Hepatitis C Virus Genome RNA", *J. of Virology* 1996, 70(6):3363-3371 ("Kolykhalov");

(4) Claims 51-53 and 62-64 have been rejected as obvious over Kolykhalov in further view of Ahern;

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[2] This reference has been cited in the Office Action by the internet web page: www.thescientist.library.upenn.edu/yr1995/july/tools_950724.htlm, December 22, 1998.

(5) Claims 14, 16-26 and 40-42 have been rejected as obvious over U.S. Patent No. 5,837,463 issued November 17, 1998 to Tanaka *et al.* ("Tanaka") and over Encke *et al.*, "Total Chemical Synthesis of the 3' Untranslated Region of the Hepatitis C Virus with Long Oligodeoxynucleotides", *J. of Virological Methods* 1998, 74:117-121 ("Encke");

(6) Claim 15 has been rejected as being obvious over Tanaka and Encke further in view of U.S. Patent No. 5,846,704 issued December 8, 1998 to Maertens *et al.* ("Maertens");

(7) Claims 27-39 have been rejected as being obvious over either Maertens or Han in view of either Kolykhalov or Tanaka and Encke; and

(8) Claims 44, 46, 48, 55, 57 and 59 have been rejected as being obvious over either Maertens or Han in view of either Kolykhalov or Tanaka and Encke, and in further view of Ahern.

Each of these rejections is discussed in turn below.

A. *The legal standard for obviousness under 35 U.S.C. § 103(a):*

Three basic criteria must be met to establish a *prima facie* case for obviousness under 35 U.S.C. § 103(a). First, there must be a concrete suggestion or motivation to modify what is taught in a reference or to combine its teachings with other references. Second, there must have been a reasonable expectation that the

modifications or combination would succeed. Finally, the combined or modified prior art must actually teach all of the claimed limitations. The motivation and the reasonable expectation of success must be found in the prior art and not in Applicants' disclosure. See, M.P.E.P § 2143, citing *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Obviousness can only be established by combining or modifying the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so, found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. M.P.E.P. § 2143.01. See also, *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USQP2d 1941 (Fed. Cir. 1992). The mere fact that references may be combined or modified does not render the resulting combination obvious, unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 143 (Fed. Cir. 1990).

Here, the relevant inquiry is whether, at the time this application was filed, one of ordinary skill in the art would be motivated to modify and/or combine the teachings in the above-cited references. If one skilled in the art would have been so motivated, it most also be shown that the modification or combination would teach or suggests *every* element of the claimed invention so that the invention, as a whole, would be apparent to the ordinarily skilled artisan. M.P.E.P. § 2143.03. The invention must be apparent with a reasonable expectation of success. M.P.E.P. § 2143.02. Thus, modification and/or combination of the above-cited references must render the

particular oligonucleotide sequences recited in the pending claims apparent to the skilled artisan and, moreover, the skilled artisan must have a reasonable expectation that primers and/or probes having those particular sequences can successfully detect or amplify HCV nucleic acids.

The initial burden is on the examiner to provide some suggestion of the desirability of doing what the inventor has done. In particular, the cited references must expressly or impliedly suggest the claimed invention, or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references. M.P.E.P. § 2142; citing *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985).

As explained in detail below, the present Office Action does not satisfy these requirements and therefore fails to establish a *prima facie* case for obviousness. In particular, none of the references cited in the Office Action, either alone or in combination, provides or suggests the particular oligonucleotide sequences used in this invention. Moreover, given only the references cited in the Office Action and without the teachings of this application, a skilled artisan could not know *a priori* that any of the particular oligonucleotides recited in the pending claims may be used to successfully amplify and/or detect HCV nucleic acids. Thus, the skilled artisan could not have a reasonable expectation of success. The rejections for obviousness should therefore be withdrawn.

B. *The claimed invention is not obvious over Han:*

Claims 1, 3-13 and 40-42 have been rejected as obvious over Han *et al.*, "Characterization of the Terminal Regions of Hepatitis C Viral RNA: Identification of Conserved Sequences in the 5' Untranslated Region and Poly(A) Tails at the 3' End", *Proc. Natl. Acad. Sci. U.S.A.* 1991, 88:1711-1715 ("Han"). In particular, Han allegedly teaches a genomic sequence from the 5' untranslated region (UTR) of the hepatitis C virus (HCV). According to the Office Action, Han further teaches that this sequence is highly conserved among viral isolates, and suggests that the sequence might be used as an HCV-specific probe. However, the Han reference does not provide oligonucleotide sequences for any particular probe or primer for this 5'-UTR, let alone the particular oligonucleotide sequences of this invention.

The Examiner maintains that, given such teaching, a skilled artisan would have been motivated to use oligonucleotide primers derived from the 5' UTR region to detect HCV and that, accordingly, primers recited in the pending claims that are derived from the 5' UTR region (*e.g.*, SEQ ID NOS:1-7) would have been *prima facie* obvious to one of ordinary skill in the art.

In response, Applicants submit that neither the particular oligonucleotide sequences of this invention nor their use (*e.g.*, to detect or amplify HCV nucleic acids) would have been obvious to one skilled in the art given only the teaching of Han and without the teaching of this application. In particular, the Examiner's attention is invited to Chapter 15.1, "Enzymatic Amplification of DNA by PCR: Standard Procedures and

Optimization" from Ausubel *et al.* (Eds.), *Current Protocols in Molecular Biology*, Vol. 3 (John Wiley & Sons, 1998) pages 15.1.1-15.1.15 ("Ausubel"), which is attached hereto as Exhibit B. This reference specifically teaches that primer selection for PCR assays is:

> "the factor that is least predictable and most difficult to trouble shoot. Simply put, some primers just do not work."

See, in particular, page 15.1.7 of Ausubel in the left hand column under the heading "Primer Selection".

Next, Applicants respectfully direct the Examiner's attention to the attached reference by Nolte *et al.*, "Preclinical Evaluation of AMPLICOR Hepatitis C Virus Test for Detection of Hepatitis C Virus RNA" *Journal of Clinical Microbiology* 1995, 33:1775-1778 (Exhibit C). Nolte describes Roche Molecular Systems's AMPLICOR HCV test; a combined RT-PCR assay for detecting HCV RNA (see the first full paragraph in the right hand column on page 1775 of Nolte). In particular, Nolte teaches that both the AMPLICOR HCV test and another assay (the SRT-PCR assay) use primers derived from the highly conserved 5'-UTR of the HCV genome (See, for example, under the headling "SRT-PCR" in the left hand column on page 1776. See, also, lines 2-6 of the right hand column on page 1776).

The present application as originally filed presents data from several experiments in which 5' HCV amplification primers of this invention are compared to the Roche AMPLICOR assay. Surprisingly, these data show that the probes and/or primers of the present invention demonstrate superior sensitivity when compared to the Roche

AMPLICOR assay. For instance, Example 1 (on pages 19-26 of the application as filed) compares HCV detection rates in clinical samples from Brazilian and Egyptian patients carrying certain HCV genotypes which are relatively rare in the United States (see, in particular, lines 12-16 on page 22 of the application as filed). The results of these experiments are provided in Tables 5 and 6 (pages 24-25) of the application, showing that "[a]ll of the primers of the invention demonstrated superior sensititivity when compared to the Roche Amplicor assay" (lines 7-8 on page 25 of the application as filed). See, also, page 26 at lines 9-10; and Example 2 (pages 26-28), particularly at lines 1-3 on page 28 of the application as filed. Thus, not only do the probes and primers have the unexpected property of successfully amplifying HCV nucleic acids (*e.g.*, in clinical samples), they do so with superior results. In particular, the probes and primers of the present invention have increased sensitivity compared with other primers used, *e.g.*, in the Roche AMPLICOR assay) that are derived from the same 5'-UTR region of the HCV genome that is taught by Han.

Given all of these teachings, the particular probes and primers recited in the pending claims of this invention cannot be obvious over Han. At best, given what is taught in Han a skilled artisan might only be motivated to try various probes and primers derived from the 5'-UTR taught by Han, and to try amplifying and/or detecting HCV nucleic acids using these various primers. Obvious to try, however, is not the standard for obviousness under 35 U.S.C. § 103(a). "Both the suggestion and the expectation of success must be found in the prior art, not in Applicant's disclosure" *In re Dow*

Chemical Co., 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). Given Ausubel's teaching that selection of PCR primers is unpredictable, a skilled artisan could not have had any reasonable expectation of success. In particular, a skilled artisan could not have expected the particular probes and primers of this invention could successfully amplify and/or detect HCV nucleic acids, much less do so with superior results compared to other primers from the same region (as in the Roche AMPLICOR assay). Accordingly, the present invention is not obvious over the Han reference cited in the Office Action.

C. *The combination of Han and Ahern does not render the claimed invention obvious:*

Claims 43, 45, 47, 49-50, 54, 56, 58 and 60-61 have been rejected under 35 U.S.C. § 103(a) as being obvious over the Han reference (discussed *supra*) in view of Ahern, "Biochemical Reagent Kits Offer Scientists Good Return on Investment", *The Scientist* 1995, 9(15):20 ("Ahern"). The Office Action indicates that, given the teachings of Ahern, it would have been obvious for one of ordinary skill in the art to incorporate the nucleotide reagents of this invention (which the Examiner contends are rendered obvious by Han) into a prepackaged kit.

The Han reference has been discussed in detail above. In particular and as also discussed above, this reference merely teaches a genomic sequence from the 5' untranslated region (UTR) of the hepatitis C virus (HCV). However, the reference does not teach or suggests any of the particular nucleotide probes or primers recited in

the pending claims of this application and cannot render such oligonucleotide sequences obvious.

Ahern does not overcome any Han's deficiencies. Instead, Ahern merely teaches the general advantage of prepackaged kits of biological reagents. However, Ahern does not teach or suggest any prepackaged PCR kit, much less a kit containing the particular probes and primers of this invention.

A *prima facie* case of obviousness requires that *all* of the claimed limitations be found in the prior art. See, M.P.E.P. § 2143.03. As explained above, however, the Han and Ahern references do not teach or suggest the presently claimed invention. In particular, these references do not teach or suggest the particular nucleic acid primers or probes of this invention. Nor do the references teach or suggest kits the contain either these or any other nucleic acid primer or probe. Accordingly, the present invention is not obvious over the Han reference cited in the Office Action, either alone or in view of Ahern.

D. *The claimed invention is not obvious over Kolykhalov:*

Claims 14, 16-26 and 40-42 are also rejected under 35 U.S.C. § 103(a) as being unpatentable over the reference Kolykhalov *et al.*, "Identification of a Highly Conserved Sequence Element at the 3' Terminus of Hepatitis C Virus Genome RNA", *J. of Virology* 1996, 70(6):3363-3371 ("Kolykhalov"). In particular, Kolykhalov allegedly teaches a sequence at the 3'-terminus of HCV genome RNA, as well as particular

oligonucleotide probes and primers derived from this region. The Examiner maintains that, given such teaching, a skilled artisan would have been motivated to use oligonucleotide primers derived from this 3'-terminal region to detect HCV and that, accordingly, oligonucleotide probes and primers that are derived from this 3'-terminal region would have been *prima facie* obvious to one of ordinary skill in the art, including certain oligonucleotides recited in the pending claims for this application (*e.g.*, SEQ ID NOS:8-9 and 14-15).

In response, Applicants respectfully submit that neither the particular oligonucleotide sequences of this invention nor their use (*e.g.*, to detect or amplify HCV nucleic acids) would have been obvious to one skilled in the art given only the teaching of Kolykhalov and without the teaching of this application. In particular, Applicants again respectfully direct the Examiner's attention to Chapter 15.1 of the Ausubel reference attached hereto as Exhibit B. As noted above, this reference specifically teaches that primer selection for PCR assays is unpredictable and that "some primers just do not work." See, in particular, page 15.1.7, left hand column under the heading "Primer Selection".

The present application as originally filed presents data from several experiments in which 3' HCV amplification primers of the invention are compared to other PCR assays known in the art. For instance, Example 3 (on page 29 of the application as filed) compares HCV detection rates in clinical samples from Brazilian patients using 3' HCV primers of this invention and the Roche AMPLICOR assay.

Example 4 (on page 30 of the application as filed) compares HCV detection rates among clinical samples using 3' HCV primers of this invention and another PCR assay referred to as the Rochester General Hospital (RGH) 5' NCR Nested PCR Assay. The results of these two experiments are presented in Table 11 (page 29) and Table 12 (page 30), respectively, of the application. These results demonstrate that "the detection system of the present invention is both sensitive and specific when compared with the [other] PCR system[s]" and that the present invention offers advantages over such prior systems because "there is less chance of carryover than when performing nested PCR." See, lines 20-24 on page 30 of the application as filed.

Given all of these teachings, the particular probes and primers recited in the pending claims of this application cannot be obvious over Kolykhalov. At best, given what is taught in Kolykhalov a skilled artisan might only be motivated to try various probes and primers derived from the 3'-terminal sequence taught by Kolykhalov, and to try amplifying and/or detecting HCV nucleic acids using these various probes and primers. Obvious to try, however, is not the standard for obviousness under 35 U.S.C. § 103(a). "Both the suggestion and the expectation of success must be found in the prior art, not in Applicant's disclosure." *In re Dow Chemical Co.*, cited *supra*. Given Ausubel's teaching that selection of PCR primers is unpredictable, a skilled artisan could not have had any reasonable expectation of success. In particular, a skilled artisan could not have expected the particular probes and primers of this invention could successfully amplify and/or detect HCV nucleic

acids. Accordingly, the present invention is not obvious over the Kolykhalov reference cited in the Office Action.

E. *The combination of Kolykhalov and Ahern does not render the claimed invention obvious:*

Claims 51-53 and 62-64 have been rejected under 35 U.S.C. § 103(a) as being obvious over the Kolykhalov reference further in view of Ahern. In particular, the Examiner contends that, given the teachings of Ahern, it would have been obvious for one of ordinary skill in the art to incorporate the nucleotide reagents of this invention (which the Examiner contends are rendered obvious by Kolykhalov) into a prepackaged kit.

Both the Kolykhalov and the Ahern references have been discussed in detail above. In particular and as also discussed above, the Kolykhalov reference merely teaches a genomic sequence from the 3'-terminal region of hepatitis C virus (HCV). However, the reference does not teach the particular nucleotide probes or primers recited in the pending claims of this application, and cannot render such probes and/or primers obvious.

Ahern does not overcome any of Kolykhalov's deficiencies. As discussed above, Ahern merely teaches the general advantages of prepackaged kits of biological reagents and does not teach or describe any PCR kit, much less kits containing the particular oligonucleotides of this invention. Accordingly, the present invention is not

obvious over the Kolykhalov reference cited in the Office Action, either alone or in view of the Ahern reference.

F. *The invention is not obvious over either Tanaka or Encke:*

Claims 14, 16-26 and 40-42 have also been rejected under 35 U.S.C. § 103(a) as being obvious over both U.S. Patent No. 5,837,463 issued November 17, 1998 to Tanaka *et al.* ("Tanaka") and over Encke *et al.*, "Total Chemical Synthesis of the 3' Untranslated Region of the Hepatitis C Virus with Long Oligodeoxynucleotides", *J. of Virological Methods* 1998, 74:117-121 ("Encke"). In particular, these references allegedly teach a 3' untranslated region of hepatitis C virus and/or certain nucleic acid primers and probes derived therefrom. However, neither of the references teaches or suggests any of the particular primers or probes recited in the pending claims of this application. Nor are the particular nucleic acid primers and/or probes of this invention obvious given only the teaching of Tanaka and/or Encke.

As discussed in detail above, at the time this application was filed it was generally recognized in the art that selection of particular PCR primers was unpredictable (see, *e.g.*, the Ausubel reference attached hereto as Exhibit A and discussed *supra*). Accordingly, the particular probes and primers of the present invention cannot be obvious over either Tanaka or Encke. Specifically, given what is taught in Ausubel, a skilled artisan could not, at the time this application was filed, have had any reasonable expectation that the particular probes and primers of the invention

would successfully amplify and/or detect HCV nucleic acids. At best, given what is taught in Tanaka and Encke a skilled artisan might only be motivated to try various probes and primers designed from the 3'-UTR taught in those references. As explained above, however, obvious to try is not the standard for obviousness under 35 U.S.C. § 103(a). Rather, the skilled artisan must also have had a reasonable expectation of success. Given Ausubel's teaching that selection of PCR primers is unpredictable, a skilled artisan could not have had any reasonable expectation of success. Accordingly, the present invention is not obvious over either the Tanaka or the Encke references, alone or in combination with each other.

G. *The combination of either Tanaka or Encke and Maertens does not render the claimed invention obvious:*

Claim 15 has been rejected under 35 U.S.C. § 103(a) as being obvious over Tanaka and Encke (discussed *supra*) further in view of U.S. Patent No. 5,846,704 issued December 8, 1998 to Maertens *et al.* ("Maertens"). The references of Tanaka and Encke have been discussed in detail above. Maertens allegedly teaches a method of genotyping HCV isolates using probes targeting sequences from the 5'-UTR of HCV and, in particular, using random primers. However, Maertens does not teach or suggest any of the particular nucleic acid probes and primers of the invention and therefore does not overcome the deficiencies of Tanaka and Encke. Accordingly, the pending claims of this application are not obvious over either Tanaka and Encke, either alone or in combination with each other and/or Maertens.

H. *Maertens and/or Han do not render the claimed invention obvious when combined with either Kolykhalov or Tanaka and Encke:*

Claims 27-39 have been rejected under 35 U.S.C. § 103(a) as being obvious over either Maertens or Han in view of either Kolykhalov or Tanaka and Encke. Each of these references has been discussed in detail, *supra*, in connection with the other obviousness rejections. In particular, the references disclose genomic sequences from either the 5'-UTR or 3'-terminal region of HCV. According to the Office Action, these references also teach or suggest oligonucleotide probes or primers derived from these regions. The Examiner therefore contends that it would have been obvious to combine the teachings of these references and design a method for detecting HCV nucleic acids using probes and/or primers from both the 5'-UTR and the 3'-terminal genomic regions of HCV.

Applicants respectfully submit, in response, that none of these references nor any combination thereof suggest the particular oligonucleotides of this invention. As discussed *supra*, the design of oligonucleotide probes and primers was not predictive at the time this application was filed. "Simply put, some primers just do not work." See the left hand column on page 15.1.7 of the Ausubel reference (Exhibit B), under the heading "Primer Selection."

Therefore, even assuming *arguendo* that it would have been obvious for a skilled artisan to combine the teachings of these references, such a combination would not provide the presently claimed invention. In particular, such a combination might, at best, only motivate the skilled artisan to try detecting HCV using primers specific for

both the 5'-UTR and 3'-terminal regions of that virus. However, the combination does not teach or suggest any of the particular oligonucleotide sequences used in the compositions and methods of this invention. Moreover, given that the design of PCR primers and probes is unpredictable (see, *e.g.*, Ausubel *supra*), the skilled artisan could not, without benefit of the teaching in this application, have any reasonable expectation of success. In particular, the skilled artisan could not reasonably expect that the particular oligonucleotide sequences recited in the pending claims of this application could be used successfully to detect HCV nucleic acids. Accordingly, the present invention is not obvious over any of the references of Maertens, Han, Kolykhalov, Tanaka or Encke, either alone or in combination.

I. *Combinations of the references of Maertens, Han, Kolykhalov, Tanaka, Encke and Ahern do not render the claimed invention obvious:*

Claims 44, 46, 48, 55, 57 and 59 have been rejected under 35 U.S.C. § 103(a) as being obvious over either Maertens or Han, in view of either Kolykhalov or Tanaka and Encke, and further in view of Ahern. Each of these references has been discussed in detail, *supra* in connection with the other obviousness rejections. In particular, the references of Maertens, Han, Kolykhalov, Tanaka, Encke and Ahern all allegedly teach genomic sequences from either the 5'-UTR or the 3'-terminal region of HCV and or certain oligonucleotide probes or primers from those regions. However, the references do not teach or suggest any of the particular oligonucleotide sequences used in the methods and compositions of this invention and, as explained above, these

particular oligonucleotide sequences cannot be obvious over any combination of those references.

Ahern does not overcome any of the deficiencies of the other referneces cited in this rejection. In particular and as discussed *supra*, Ahern merely teaches general advantages offered by prepackaged kits of biological reagnets. Ahern does not teach or describe a PCR kit, much less kits containing the particular oligonucleotide sequences of this invention.

Accordingly, the present invention is not obvious over any of the references of Maertens, Han, Kolykhalov, Tanaka or Encke, either alone or in combination with each other and/or Ahern.

Applicants submit that each of the rejections under 35 U.S.C § 103(a) has been obviated by the above remarks. In particular and as explained in detail above, none of the rejections satisfies the requirements necessary to establish a *prima facie* case for obviousness under 35 U.S.C. § 103(a). Accordingly, Applicants respectfully request that all of the rejections under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

For the reasons state above, Applicants believe that the pending claims of this application, as amended, are in condition for allowance. Accordingly, withdrawal of all objections and rejections and reconsideration of the application are respectfully requested. The

Examiner is invited to contact Applicants' representative at the below-indicated telephone number if (s)he believes it would advance prosecution of the application. An allowance is earnestly sought.

Respectfully submitted,

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Samuel S. Woodley, III
Reg. No. 43,287
Agent for Applicants

DARBY & DARBY, P.C.
805 Third Avenue
New York, N.Y. 10022
Phone (212) 527-7700